

REMARKS

The Notice to Comply mailed October 1, 2002, has been received and reviewed. Responsive thereto, the Brief Description of Drawings section of the application has been amended to identify the sequence identifiers of FIGS. 2, 4, 7A and 7B that were added to the drawings in the Amendment filed July 23, 2002. The sequence identifiers and corresponding sequences were included in the Substitute Sequence Listing filed July 23, 2002. For convenience, a copy of the Substitute Sequence Listing and the corrected drawings are enclosed herein. Reconsideration is respectfully requested.

CONCLUSION

Should the Office determine that additional issues remain which might be resolved by a telephone conference, it is respectfully invited to contact applicants' undersigned attorney.

Respectfully submitted,



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Enclosures: copy of Substitute Sequence Listing and drawing corrections filed July 23, 2002

Document in ProLaw

MARKED UP VERSION SHOWING CHANGES MADE

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1: Schematic drawing of the pBr/Ad.Bam-rITR construct.

FIG. 2: Schematic drawing of the strategy used to delete the fiber gene from the pBr/Ad.Bam-rITR construct, using primers NY-UP (SEQ ID NO: 36) and NY-DOWN (SEQ ID NO: 37).

FIG. 3: Schematic drawing of construct pBr/Ad.BamRDfib.

FIG. 4: Nucleotide [Sequence] sequence of chimaeric fiber Ad5/16, SEQ ID NO: 32.

FIG. 5: Schematic drawing of the construct pClipsal-Luc.

FIG. 6: Schematic drawing of the method to generate chimaeric adenoviruses using three overlapping fragments. Early (E) and late regions (L) are indicated. L5 is the fiber coding sequence.

[FIG. 7] FIGS. 7A & 7B: Sequences including the gene encoding adenovirus 16 fiber protein as published in Genbank with nucleotide sequence SEQ ID NO: 33 and amino acid sequence SEQ ID NO: 35; and sequences including a gene encoding a fiber from an adenovirus 16 variant as isolated in the present invention with nucleotide sequence SEQ ID NO: 38 and amino acid sequence SEQ ID NO: 34, wherein the sequences of the fiber protein are from the NdeI-site. FIG. 7A nucleotide sequence [comparison] comparisons of SEQ ID NO: 33 and SEQ ID NO: 38. FIG. 7B amino-acid [comparison] comparisons of SEQ ID NO: 35 and SEQ ID NO: 34.

FIG. 8 : Infection of synoviocytes using different amounts of virus particles per cell (MOI) and two different adenoviruses: Ad5=Ad5.Clip.Luc; Ad5/16= Ad5.Luc-fib16. Luciferase transgene expression, 48 hours after a 2 hours infection procedure is depicted as relative light units (=RLU) per microgram whole cell lysate. Error bars represent standard error of the mean (SEM).

FIG. 9: Infection of synoviocytes using different concentrations of cells. Luciferase transgene expression, 48 hours after a 2 hours infection procedure is depicted as relative light units (=RLU) per microgram total protein. Error bars represent SEM. The actual MOI differed between the cell concentrations and ranged from [20.000] 20,000 virus particles per cell (cell

density [12.500] 12,500) to [2.500] 2,500 virus particles per cell (cell density [100.000]
100,000).

FIG. 10: Infection of synoviocytes using different virus exposure periods. Luciferase transgene expression, 48 hours after either a 2 hours or a 20 hours virus exposure is depicted as relative light units (=RLU) per microgram protein. Error bars represent standard deviations.

FIG. 11: Synoviocytes were incubated with IG.Ad.CMV.TK or IG.Ad.mlp-I.TK. Cells were cultured with or without GCV.

FIG. 12: Bystander killing was assessed in cultures containing both TK-infected and non-TK-infected synoviocytes in a proportion 0/100, 50/50, 25/75 and 0/100. Cells were cultured with or without GCV.

FIGs. 13 A & B: X-gal expression in synovial tissue 3 days after intra-articular injection of IG.Ad.CMV.lacZ in the knee. 13A: macroscopy. 13B: direct LacZ staining of synovial tissue counterstained with Mayers Hamalanlosung.

FIG. 14 is a graph comparing infection of Ad5.luc and Ad5.fib16.luc on RA synoviocytes.

FIG. 15 is a graph depicting the percentage of lacZ positive cells with Ad5.lacZ and Ad5.fib16.lacZ in RA synoviocytes.

FIG. 16 A & 16B are graphs depicting the infection efficiency of Ad5.GFP and Ad5.fib16.GFP in RA synoviocytes and the respective luciferase counts respectively.

FIG. 17 is a graph depicting the infectivity of chimeric adenoviruses on RA synoviocytes.

FIG. 18A is a graph depicting the percentage of infected cells with three B-type fiber-modified viruses on RA synoviocytes.

FIG. 18B is a graph depicting GFP production with three B-type fiber-modified viruses on RA synoviocytes.

FIG. 19 is a graph depicting the comparison of three B-type fiber-modified adenovirus for infectivity on RA synoviocytes.

FIG. 20 is a graph depicting the comparison of infectivity Ad5.lacZ vs. Ad5.fib16.lac6 in RA synoviocytes from six patients.